THE INFLUENCE OF VARIOUS STEROIDS ON THE DEVELOPMENT OF CASTRATION CHANGES IN THE HYPOPHYSIS OF THE RAT

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It is well known that the development of castration changes in the rat pituitary can be prevented by the administration of estrane derivatives with folliculoid [2] activity or androstane derivatives possessing testoid properties. However, the relevant literature contains many puzzling observations. Some investigators (Fluhmann and Kulchar, '31) found "estrin" practically ineffective in this respect, whence they concluded that another ovarian factor must be responsible for the maintenance of the normal pituitary structure in intact females. Other workers (Lehmann, '27; Martins, '31), using rather crude preparations, believed that the "testis hormone" is inactive, or at least only very slightly active, in spayed females although it is effective in castrate males. Similar negative results have been obtained with small doses of androsterone in the spayed female rat (Reece, '41). Conversely it has been claimed that folliculoid preparations are ineffective in the castrate male (Lehmann, '27; Desclin, '34; Yanagita, '37). These observations implied that this effect is, in a sense, sex-specific. Early investigators, who used impure corpus luteum preparations, which were not entirely free

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[2] These terms are used here in accordance with the recently proposed terminology of the steroid hormone actions (Selye, '41) instead of the rather clumsy terms "estrogenic" or "follicular hormone-like," "adrenal cortical hormone-like," "corpus luteum hormone-like" or "progestational" and "testis hormone-like" or "androgenic."

of folliculoid activity, concluded that the corpus luteum hormone prevents the development of castration changes at least in the spayed female (Charipper, '34; Clauberg and Breipohl, '34, '35). However, with the exception of Brooksby ('38), all those workers who used pure synthetic progesterone considered it to be ineffective both in male and in female gonadectomized rats (Hohlweg, '35; Migliavacca, '36; Cutuly, '41). Masson et al. ('42) studied the action of three 17-ethyl-etiocholane (pregnane) derivatives on the pituitary of spayed female rats. They found that acetoxy-pregnenolone (21-acetate of 17-ethyl-Δ^5-androstene-3(β),21-diol-20-one) and pregnenolone (17-ethyl-Δ^5-androstene-3(β)-ol-20-one) prevent the deyelopment of castration changes, while pregnanedione (17-ethyl-etiocholane-3,20-dione) is ineffective. They emphasized that the first two of these steroids possess other hormonal actions inasmuch as they are both folliculoid and corticoid, while pregnanedione possesses no known hormonal action. These findings, as well as our own observations, led us to suspect that the castration-change-preventing effect of the steroids may be less specific than has hitherto been believed. It has been emphasized by Selye ('42) and Clarke and Selye ('42) that the anesthetic power and the ability to stimulate the vaginal epithelium are pharmacological actions common to all hormonally active steroids irrespective of the specific nature of their main hormonal activity. The experiments to be reported in this communication indicate that the castration-change-preventing effect is also shared by all hormonally active steroids which have so far been tested for this action in adequate doses. Conversely, steroids devoid of any known hormonal effect do not prevent the formation of castration cells.

EXPERIMENTAL

All steroids were administered either in true solution or in fine crystalline suspension depending on their solubility. The relevant experimental details are mentioned in table 1 which is almost self-explanatory. It should be emphasized that not

all these experiments were performed primarily for the study of castration changes. This is why the dosage and the length of treatment is not uniform in all groups. But since the pituitaries were always taken for section, the material is quite satisfactory for the study of the problem under consideration here. The full systematic name of each steroid is given in order to avoid confusion and in those cases in which the compound is generally referred to by a common name, the latter is given in block letters. The melting point of the sample which was available to us for these experiments, was determined in our laboratory and is given in the table as an indicator of the degree of purity of the preparation used. The melting point will also facilitate identification of a compound whenever there is doubt about several possible isomerids.

Perusal of the table clearly indicates that all the hormonally active steroids (compounds 1–12) tested in this series, exhibit the castration-change-preventing effect both in the male and in the female animal. It will be noted that our series includes folliculoid (compounds 1 and 2), testoid (compounds 3, 4, 5, 6, 7, and 12), luteoid (compounds 8 and 12) and corticoid (compounds 9 and 11) substances as well as a steroid whose predominant pharmacological action is to prevent testis atrophy in the hypophysectomized animal (compound 10). For a more detailed review of the literature concerning the hormonal activities of these steroids the reader is referred to the recent article of Selye ('42), but even a cursory study of the chart clearly indicates that the castration-change-preventing action is shared by all hormonally active steroids so far examined. Even though quantitatively some of these may be more active than others, qualitatively the effect is independent of the specific nature of the main hormonal action. Conversely, the hormonally inactive steroids (compounds 13, 14 and 15) are unable to prevent the development of castration changes even if they are chemically very closely related to true hormones. This is clearly shown in the case of pregnanedione (compound 15) which differs from proge-

TABLE 1

Effect of various steroids on the development of castration cells in the anterior pituitary of castrate male and female albino rats.

NO. OF COMPOUND	STEROID	MALE						FEMALE				
		M.P. °C.	Dose in mg./day	Days after castration [2]	No. of animals	Initial body weight in grams	Prevention of castration changes [1]	Dose in mg./day	Days after castration [2]	No. of animals	Initial body weight in grams	Prevention of castration changes [1]
1	$\Delta^{1,3,5}$-estratriene-3,17(α)-diol *-ESTRADIOL*	176	2	11 (0)	5	48	3					
2	$\Delta^{1,3,5}$-estratriene-3-ol-17-one *ESTRONE*	254–256						0.2	13 (2)	3	122	3
3	Δ^{4}-androstene-3-one-17(α)-ol-propionate *TESTOSTERONE PROPIONATE*	118	1	23 (2)	2	160	3					
4	Δ^{4}-androstene-3,17-dione	169–171						4	20 (2)	6	76	3
5	Δ^{5}-androstene-3(β)-17(α)-diol	182–183	2	11 (0)	5	47	2	1	30 (4)	7	82	3
			10	11 (0)	6	46	3					
6	Δ^{5}-androstene-3(β)-ol-17-one *DEHYDRO-ISO-ANDROSTERONE*	137	2	11 (0)	5	47	1					
			10	11 (0)	6	48	3					
7	17-methyl-Δ^{4}-androstene-3-one-17(α)-ol *METHYL TESTOSTERONE*	153	2	11 (0)	4	49	2	4	30 (4)	5	73	3
			10	11 (0)	2	50	3					
8	17-ethyl-Δ^{4}-androstene-3,20-dione *PROGESTERONE*	128	10	11 (0)	6	48	3	15	13 (2)	3	136	2
			10	20 (2)	3	161	3					
			10	21 (0)	2	248	3					

9	17-ethyl-Δ^4-androstene-3,20-dione-21-ol-acetate *DESOXYCORTICOSTERONE ACETATE*	152	10	11 (0)	6	40	2					
10	17-ethyl-Δ^5-androstene-3(β)-ol-20-one Δ^5-*PREGNENOLONE*	186	10	11 (0)	5	47	3	4	30 (4)	4	78	3
								5	33 (10)	3	80	3
11	17-ethyl-Δ^5-androstene-3(β),21-diol-20-one-21-acetate *ACETOXYPREGNENOLONE*	183–184						3	33 (2)	3	60	3
12	17-ethinyl-Δ^4-androstene-3-one-20-ol *ETHINYL TESTOSTERONE*	265–268	2	11 (0)	5	48	2	4	20 (2)	6	75	2
			10	11 (0)	6	46	3					
			3	23 (2)	2	168	2					
13	17-iso-octyl-Δ^5-androstene-3(β)-ol *CHOLESTEROL*	149						4	30 (4)	7	78	0
14	17-iso-decyl-$\Delta^{5,22}$-androstadiene-3(β)-ol *STIGMASTEROL*	168–169	10	11 (0)	6	46	0					
15	17-ethyl-etiocholane-3,20-dione *PREGNANEDIONE*	190	10	11 (0)	5	47	0	3	33 (10)	4	80	0
16	Not treated	....	..	22	1	39	0	..	13	3	129	0
			..	23	6	162	0	..	33	4	80	0
			..	25	11	114	0					

[1] Graded 0–3: 0, indicates no difference between treated and controls; 1, a distinguishable difference; 2, an almost complete absence of castration changes; 3, complete absence of castration changes.

[2] The figures in brackets indicate the number of days which elapse between gonadectomy and the first of the daily injections.

sterone (compound 8) only in that the latter possesses a double bond between C_4 and C_5, yet pregnanedione is quite inactive while progesterone is highly effective in preventing the development of castration cells in the pituitary. It should be emphasized that, unlike the true hormonal activities, anesthetic potency does not necessarily endow a compound with the ability to prevent castration cell formation. This is shown by the same example of pregnanedione which is more potent as an anesthetic than any other steroid enumerated in our table and yet is devoid of the castration cell inhibitory action.

SUMMARY

Fifteen steroid compounds have been studied for their ability to prevent the development of castration cells in the pituitary of gonadectomized rats. It was found that irrespective of their predominant hormonal action, all folliculoid, testoid, corticoid and luteoid compounds, as well as pregnenolone — whose predominant action appears to be to stimulate testis growth — share the ability to inhibit the formation of castration cells in the hypophysis of the male or female gonadectomized rat. The hormonally inactive steroids have no such effect.

It is concluded that judged by the evidence available up to date, the castration-change-preventing effect is a common pharmacological action shared by all hormonally active steroids.

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